



Study of prognostic value of various biomarkers (creatinine phosphokinase - MB, C - reactive protein) and admission neutrophil lymphocyte ratio in early outcome of patients with acute myocardial infarction

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Abstract

Introduction: Coronary artery disease (CAD) continues to be a major cause of morbidity and mortality in developed as well as developing countries. The time course of bio-marker (protein) release during acute myocardial infarction provides diagnostic information which in turn is helpful in evaluating therapeutic interventions. The three easily measurable markers e.g. creatinine phosphokinase - MB (CPK-MB), C -reactive protein (CRP) and neutrophil lymphocyte ratio (N: L) in patients of acute myocardial infarction (AMI) can be used for diagnosis as well as prognosis.

Material and methods: Patients of acute myocardial infarction admitted in intensive coronary care unit (ICCU) of a General Hospital were included in the present study. Detailed clinical examination of each patient was done and after initiating oxygen inhalation and pain relieving therapy, following



investigations were sent; hemoglobin level, total white blood cell (WBC) count, differential count, CPK -MB, CRP level.

Observation: Significantly high CPK - MB levels (>60 IU/L) were observed in 24% of patients who had or later developed complication of MI while only 7% of uncomplicated MI patients had significantly elevated levels of CPK - MB. Similarly more patients in complicated MI had higher values of CRP and N: L ratio as compared to uncomplicated MI patients.

Conclusion: Blood levels of biomarker CPK - MB and inflammation markers CRP and N: L ratio at the time of hospital admission does have a direct correlation with chances of development of complications and/or mortality in early post-infarct period. These bio-chemical markers are important not only for diagnosis but also have prognostic values and help in risk stratification and decision making regarding further early therapeutic intervention.

Key words

Biomarkers, Inflammation, Myocardial infarction, Prognosis.

Introduction

Coronary artery disease (CAD) continues to be a major cause of morbidity and mortality developed as well as developing countries. The extent of myocardial damage after an acute myocardial infarction (AMI) determines the prognosis for morbidity and mortality in early post-infarct period, as also the overall quality of life afterwards. The diagnosis of an acute myocardial infarction is based on symptoms, electrocardiographic changes and bio-markers. The first enzyme marker SGOT (serum glutamate oxaloacetic transaminase) used as an aid for detection of myocardial necrosis was reported before about 50 years and since then many more markers have been and are being added with more and more specificity and sensitivity [1]. The time course of bio-marker (protein) release during acute myocardial infarction provides diagnostic information which in turn is helpful in evaluating therapeutic interventions (mechanical or pharmacological).

Measurement of release of those biomarkers, inflammatory process markers e.g. neutrophil lymphocyte ratio (N: L), C – reactive protein

(CRP) etc. which have become quite a routine investigations in day to day practice in almost every hospital, is cheap and does not require any sophisticated equipment. If these parameters are done in early infarct period may serve as prognostic indicators.

Many workers in field of risk evaluation in AMI have reported that leukocytosis and increase in neutrophil lymphocyte ratio and CRP measurement on admission after an AMI has been associated with increased risk of in hospital heart failure and death. Ala, et al. [2] concluded in their study that both these markers are acting independently as risk predictors for early mortality. It has also been found that admission creatine kinase is better prognostic marker for a subsequent cardiac event [3].

Considering all these aspects, we thought it worthwhile to study the prognostic value of three easily measurable markers e.g. creatinine phosphokinase – MB (CPK – MB), CRP and neutrophil lymphocyte ratio in patients of AMI on admission by correlating their values with mortality and morbidity in early post infarct period.

Material and methods

130 patients of acute myocardial infarction admitted in intensive coronary care unit (ICCU) of a General Hospital were included in the present study. Acute Myocardial Infarction was diagnosed in patients with or without ischemic chest pain by presence of ST segment elevation of > 1 mm with or without T wave inversion and Q wave in more than two consecutive limb leads or chest leads in standard 12 lead electrocardiogram (ECG). Detailed clinical examination of each patient was done and after initiating oxygen inhalation and pain relieving therapy, following investigations were sent; hemoglobin level, total WBC count, differential count, CPK - MB, CRP level. Enzopak reagent kit (Reckon Diagnostics P. Ltd.) was used for estimation of CPK - MB and values reported as IU/L. (Normal value: 0 to 25 ± 5 IU/L.) Hemoglobin level, total WBC count and differential count of patients were obtained by Abacus-3 hematology analyzer (Hungary). SS - CRP kit with immuneterbidometric method and immulite machine was used to estimate CRP levels. All the patients were kept and observed in ICCU for initial 2-3 days or more depending upon their clinical condition and then in ward for total of 5-10 days. All patients were treated with standard protocol drugs. Other therapeutic measures were used in complicated cases as per their needs. All the findings and laboratory reports were recorded in separate proforma for each patient. All the relevant findings for all patients were enlisted in a master chart. Statistical analysis of data obtained was done with help of SPSS (Statistical Package for Social sciences) version 13.0. The observations are recorded in descriptive and tabulated form.

Observation

In present study, we included all the patients admitted with AMI irrespective of site of infarct and complications.

In the present study, we found strong association between CPK - MB level and complicated MI ($p = 0.0001$). Mean admission CPK - MB level in patients with complicated MI (50.1 ± 21 IU/L) was found to be significantly higher than the mean level in patients with uncomplicated MI (40 ± 24.8 IU/L). We also found the strong association of CPK - MB level and mortality, mean admission CPK - MB level in patients who died (55.6 ± 17.3 IU/L) was found to be significantly higher than the mean level in patients who survived (42.5 ± 24.2 IU/L) ($p = 0.001$).

In 30.8% of patients CPK - MB levels were found to be within normal range and none of the patients with normal range died. While in 13%, it was significantly raised. Values of CPK - MB were found to be higher than cut off in 84.8% patients with early complication in MI. While in uncomplicated MI patients, the values were found to be high in 60.7% of patients.

In the present study, we found strong association of CRP level with complications in MI. ($p = 0.0001$). Mean admission CRP level in patients with complicated MI (4.9 ± 4.0 mg/L) was found to be significantly higher than the mean level in patients with uncomplicated MI (3.5 ± 6.8 mg/L). In 50% of patients CRP levels were found in high risk group.

In the present study, we found strong association of CRP level with mortality, mean admission CRP level in patients died (8.3 ± 5.6 mg/L) was found to be significantly higher than the mean level in patients survived (3.6 ± 5.9 mg/L) ($p = 0.0001$). Mortality in high risk group of CRP level was 15.4% where as average and low risk group CRP level has no mortality. Further in high risk group, mortality in range of 3.1 to 4.5 mg/L CRP was 6.1%, mortality in patients with CRP range of 4.6 to 6 mg/L CRP was 33.3% and in patients with above 6 mg/L

CRP level mortality was as high as 50% as per **Table - 1**.

In present study, we found strong association of N: L ratio with complications ($p = 0.004$). Mean admission N: L ratio in patients with complicated MI (4.0 ± 1) was found to be significantly higher than the mean level in patients with uncomplicated MI (3.5 ± 0.9). Rate of complications among patients in range of 0 to 2 N: L ratio was found to be 25%, in range of 2.1 to 4 it was 31% while with N: L ratio above 4 almost 44% of patients had complications. We also found strong association of N: L ratio with death, mean admission N: L ratio in patients who died (4.2 ± 0.6) was found to be significantly higher than the mean level in patients who survived (3.6 ± 1). ($p = 0.006$). Mortality among patients in range of 0 to 2 N: L ratio was nil, while in range of 2.1 to 4 it was 2.2% and in range above 4 was 21.1%. Out of 130 patients in present study, 10 patients (8 male and 2 female) died, thus mortality was 7.7%.

As per **Table - 1**, significantly high CPK - MB levels (>60 IU/L) were observed in 24% of patients who had or later developed complication of MI while only 7% of uncomplicated MI patients had significantly elevated levels of CPK - MB. Similarly more patients in complicated MI had higher values of CRP and N: L ratio as compared to uncomplicated MI patients.

Discussion

Diagnostic values of bio-markers and inflammation markers have already been established in cases of AMI since long. Presence of myocardial necrosis, increase in cortisol levels during acute stress reaction and a key role of inflammation at all stages of CAD have been considered as some of the causes respectively

for elevated CPK - MB, WBC count and CRP in AMI. Thus, higher values in patients of MI may help in decision making for consideration of further management like early angioplasty or coronary artery bypass grafting (CABG) or early transfer of patient to higher center or special care unit. We studied 101 male and 29 female patients of AMI to evaluate the prognostic implications of CPK - MB, CRP and N: L ratio on early complications and mortality.

Creatine kinase is a sensitive marker of myocardial necrosis. It is still widely used in developing countries for diagnosis for its high sensitivity and cost-effectiveness. 12% of patients in our study were admitted with early complications like left ventricular failure (LVF), arrhythmia and cardiogenic shock. CPK - MB levels were very high (more than double the normal range) in 24% of these complicated MI as compared to 7% of uncomplicated MI. Even stronger association of higher level of CPK - MB in fatal MI cases was also observed in present study as $> 50\%$ of patients who died had CPK - MB levels higher than 50 IU/L. Thus, we found strong association of CPK - MB level with morbidity and mortality both. Khawar, et al. [3] in their study also reported significant difference in values of CPK-MB between patients who survived and died. They had concluded by considering CPK-MB as a better prognostic marker for a subsequent cardiac event. Another researchers Savonitto, et al. [4] had also reported that even minor rise in CPK appeared to have important and independent prognostic implications. Results of our study correlate well with other studies.

Inflammation plays a key role at all stages in initiation and progression of coronary artery disease. The white blood cell count has been established as a marker of inflammation. Elevated white blood cell count plays an important role in the vascular injury and

atherogenesis and also in development of an atherosclerotic plaque rupture and thrombosis [5]. White blood cell (WBC) count and its subtypes have been studied as inflammatory biomarkers to predict cardiovascular outcomes in patients with and without coronary artery disease. However, little research has been made regarding any specific subtype of cells in the WBC series that could be responsible for the AMI and its outcome, neutrophils count has been related to myocardial infarct extension, development of post-infarction heart failure, impaired epicardial and micro vascular perfusion and post-infarction mortality. Lymphocytes also have a pivotal role in modulating the inflammatory response at stages of the atherosclerotic process.

In the present study increasing N: L ratio was observed to be strongly associated with fatal outcome which appeared at higher level in third tertile (21.1%) as compared to other tertiles (first tertile = 0%, second tertile = 2.2% ($p = 0.006$)). Ala, et al. [2] in their study observed highest mortality in third tertile (26.3%) as compared to the first and second tertiles (0% and 6.9%) respectively ($P < 0.05$). Thus this relatively simple and inexpensive inflammatory marker was found to be a good predictor of poor in-hospital outcome. And they also found association between N: L ratio and heart failure which was significantly associated with increasing N: L ratio ($p < 0.05$), it was also higher in the third tertile (26.3%). In the present study, we found strong association between N: L ratio and complications ($p = 0.004$) which was also more in third tertile (44.7%). Thus this very simple and routine measurement did have prognostic implication in both mortality and morbidity.

The third marker we studied in AMI patients was C - reactive protein, an acute phase reactant which takes part directly in the atherosclerotic

process and represents one of the most important predictors of vascular death. In our study, we found strong association of increasing CRP level with mortality ($p = 0.0001$). P. Ortolani, et al. [6] in their study found strong association of C - reactive protein levels measured on admission with in-hospital and long-term mortality, providing evidence for usefulness of the marker for the patient's mortality risk stratification. They found C - reactive protein value as an independent predictor of in-hospital outcome. C.M. Nagesh, et al. [7] also concluded that CRP has prognostic value.

Conclusion

From our study we drew a conclusion that blood levels of biomarker CPK - MB and inflammation markers CRP and N: L ratio at the time of hospital admission does have a direct correlation with chances of development of complications and/or mortality in early post-infarct period. We also found that all these biochemical markers are important not only for diagnosis but also have prognostic values and help in risk stratification and decision making regarding further early therapeutic intervention.

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Table – 1: CPK - MB, CRP level and neutrophil lymphocyte ratio in the patients with complicated and those having uncomplicated MI.

	CPK-MB (IU/L)			CRP (mg/L)					Neutrophil Lymphocyte ratio		
	Normal	30-60	>60	0-1.5	1.6-3	3.1- 4.5	4.6-6	>6	0-2	2.1-4	>4
Complicated MI (n=46)	07 (15.2%)	28 (60.9%)	11 (23.9%)	02 (4.3%)	13 (28.3%)	18 (39.1%)	05 (10.9%)	08 (17.4%)	01 (2.2%)	28 (60.8%)	17 (37%)
Un complicated MI (n=84)	33 (39.3%)	45 (53.6%)	06 (7.1%)	10 (11.9%)	40 (47.7%)	31 (36.9%)	01 (1.1%)	02 (2.4%)	3 (3.6%)	60 (71.4%)	21 (25%)
Death (n=10)	0	08 (80%)	02 (20%)	0	0	03 (30%)	02 (20%)	05 (50%)	0	02 (20%)	08 (80%)